

The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions

Michael A Rogawski¹ & Wolfgang Löscher²

Antiepileptic drugs (AEDs) are commonly prescribed for nonepileptic conditions, including migraine headache, chronic neuropathic pain, mood disorders, schizophrenia and various neuromuscular syndromes. In many of these conditions, as in epilepsy, the drugs act by modifying the excitability of nerve (or muscle) through effects on voltage-gated sodium and calcium channels or by promoting inhibition mediated by γ -aminobutyric acid (GABA) A receptors. In neuropathic pain, chronic nerve injury is associated with the redistribution and altered subunit compositions of sodium and calcium channels that predispose neurons in sensory pathways to fire spontaneously or at inappropriately high frequencies, often from ectopic sites. AEDs may counteract this abnormal activity by selectively affecting pain-specific firing; for example, many AEDs suppress high-frequency action potentials by blocking voltage-activated sodium channels in a use-dependent fashion. Alternatively, AEDs may specifically target pathological channels; for example, gabapentin is a ligand of $\alpha 2\delta$ voltage-activated calcium channel subunits that are overexpressed in sensory neurons after nerve injury. Emerging evidence suggests that effects on signaling pathways that regulate neuronal plasticity and survival may be a factor in the delayed clinical efficacy of AEDs in some neuropsychiatric conditions, including bipolar affective disorder.

Effective medications have been available to treat seizure disorders for nearly 150 years. Throughout the history of the modern pharmacological treatment of epilepsy, AEDs have found application for nonepileptic conditions. The most important nonepilepsy uses have been in pain medicine and psychiatry. In 2003, neurologists in the United States reported that 45% of their AED prescriptions were for conditions other than epilepsy, with migraine and neuropathic pain commanding the bulk of them. Among primary care physicians, prescriptions of AEDs for nonepilepsy conditions were higher (63%). Psychiatrists, not surprisingly, reported writing 96% of their AED prescriptions for conditions other than epilepsy, predominantly bipolar disorder and schizophrenia (S.P. Maes, Decision Resources, Waltham, Massachusetts).

Most AEDs were developed to treat epilepsy, and their therapeutic activity in other disorders was identified later. Many of the AEDs currently in use were discovered more or less fortuitously, often by screening analogs of compounds with known activity in the central nervous system¹. For example, the identification of imipramine as an antidepressant was followed by a systematic investigation of the biological activity of related iminodibenzyl compounds, resulting in the recognition that carbamoyl derivatives such as carbamazepine have antiepileptic properties². When carbamazepine was subsequently

found to be useful in trigeminal neuralgia, other types of neuropathic pain and bipolar disorder, it was assumed that these actions were the result of its structural similarity to tricyclic antidepressants; however, several AEDs with unrelated chemical structures are effective treatments for these conditions (Table 1). It therefore seems plausible that shared molecular actions underlie the efficacy of AEDs in epilepsy and nonepileptic conditions. This suggests that epilepsy, pain syndromes and affective disorders have common pathophysiological mechanisms.

Epidemiological evidence indicates that epilepsy, migraine, depression and essential tremor are comorbid conditions, such that the existence of one condition increases the risk of the others³. In particular, epilepsy and migraine are strongly associated: individuals with epilepsy are 2.4 times more likely to develop migraine than their relatives without epilepsy⁴. The comorbidity of epilepsy and other episodic neurological and psychiatric disorders suggests that these various conditions share one or more common etiologies. If this is true, it is not surprising that new AEDs often find utility in these nonepileptic disorders. In a companion article, we review the molecular and cellular mechanisms through which AEDs act to protect against seizures⁵. Here we consider the actions of AEDs in the diverse other conditions for which they are prescribed.

Sedation and anxiety

The first AEDs, bromides and phenobarbital, were used as hypnotics and sedatives before their antiepileptic effect was discovered serendipitously. Phenobarbital is still used for insomnia, although it has been largely replaced by the much safer benzodiazepines. The sedative and hypnotic effects of benzodiazepines, similar to their antiepileptic effects, are due to allosteric positive modulation of

¹Epilepsy Research Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892, USA.

²Department of Pharmacology, Toxicology, and Pharmacy, University of Veterinary Medicine, and Center for Systems Neuroscience, Hannover, Bünteweg 17, D-30559 Hannover, Germany. Correspondence should be addressed to M.A.R. (michael.rogawski@nih.gov).

Table 1 Therapeutic activities of AEDs in conditions other than epilepsy

Drug	Pain			Neuromuscular disorders						Psychiatric disorders				
	Neuro- pathic pain	Trigeminal neuralgia	Migraine prophylaxis	Non-epileptic myoclonus	Essential tremor	Myotonia	Myokymia (Isaacs' syndrome) ^a	RLS	Dystonia	Insomnia	Anxiety disorders ^b	Bipolar affective disorders		Alcohol withdrawal ^{c,d}
												Manic phase	Depressed phase	
Phenytoin	●	●				●	●		●			●		
Carbamazepine	●	● ^e				●	●		●			●		●
Oxcarbazepine	●	●					●					●		
Lamotrigine	●	●	●										●	
Zonisamide	●		●									●		
Valproate	●	●	●	●							●	●		●
Topiramate	●	●	●		●						●	●		
Gabapentin	● ^f	●	●		●			●			●			●
Levetiracetam	●		●	●										
Phenobarbital					●					●				
Primidone					●									
Benzodiazepines	●	●		●	●			●	●	●	●			●
Vigabatrin														
Tiagabine	●		●								●			

‘●’ indicates evidence from controlled trials or several open-label trials and general acceptance of utility; ‘●’ indicates less extensive base of evidence. RLS, restless legs syndrome. For details, see text and refs. 101–109. ^aAlso episodic ataxia with myokymia. ^bIncludes panic. ^cTopiramate has been shown to reduce alcohol consumption and craving in alcoholics (ref. 110). ^dCase reports suggest that carbamazepine and valproate may be useful for benzodiazepine withdrawal; topiramate may be useful for opiate withdrawal; and valproate may reduce cocaine use and craving in addicts¹¹¹. ^eCarbamazepine is approved in the United States for trigeminal neuralgia. ^fGabapentin is approved in the United States for postherpetic neuralgia. Topiramate may also be useful in the treatment of bulimia and binge eating disorder^{112,113}.

GABA_A receptors, predominantly those containing the $\alpha 1$ subunit⁶, anxiolytic effects seem to be dependent on GABA_A receptors containing the $\alpha 2$ subunit. Barbiturates also act through effects on GABA_A receptors, but they have additional actions on Ca²⁺ and Na⁺ channels⁷. Gabapentin has sedative activity, and emerging evidence suggests that it may be anxiolytic^{8–10}, although the underlying mechanism is unclear.

Neuropathic pain

Clinical trials indicate that several AEDs, including carbamazepine, phenytoin, lamotrigine, felbamate and gabapentin, are effective in neuropathic pain^{11–14}, and in paroxysmal nerve pain states such as trigeminal neuralgia¹⁵ (Table 1). Neuropathic pain results from chronic injury to sensory neurons, leading to axonal sprouting and neuroma formation. After such an injury, marked changes occur in the expression of genes encoding both Na⁺ and Ca²⁺ channels, resulting in changes in their distribution and composition.

Role of Na⁺ channels. Changes in the expression of Na⁺ channels lead to alterations in their biophysical properties and their abnormal accumulation in nociceptors and sensory nerves. This plasticity in Na⁺ channel expression is accompanied by electrophysiological changes that poise these cells to fire spontaneously or at inappropriately high frequencies, often from ectopic sites¹⁶. Among the changes accompanying injury is an increase in tetrodotoxin-sensitive Na_v1.3 (type III) Na⁺ channels in the cell bodies of sensory neurons^{17–21} (Figs. 1b and 2). In central neuropathic pain, second-order nociceptive neurons in the spinal cord dorsal horn also show hyperexcitability and an increase in Na_v1.3 expression²². Na_v1.3 produces a Na⁺ current that recovers rapidly from inactivation, permitting high-frequency ectopic firing in injured neurons²³.

Of particular importance is the redistribution of Na_v1.8 and Na_v1.9 from the sensory neuron soma to the peripheral axon at the site of injury (Fig. 2). Na_v1.8 and Na_v1.9 are sensory neuron-specific,

tetrodotoxin-resistant Na⁺ channel α subunits that are thought to be required for neuropathic pain. Recent evidence indicates that increased expression of Na_v1.8 in uninjured peripheral axons and nociceptors near the site of injury results in spontaneous ectopic discharges and lowers the threshold for mechanical activation, which is thought to underlie the paraesthesias, hyperalgesia and allodynia characteristic of painful neuropathies^{21,24,25}.

Another potentially important change occurs in the expression of $\beta 3$ (an auxiliary Na⁺ channel subunit), which, like Na_v1.8, is mainly expressed in small-diameter pain neurons^{26,27} (Fig. 2). Nerve injury is associated with increased $\beta 3$ mRNA in these neurons. Because heteromeric Na⁺ channels consisting of Na_v1.8 and $\beta 3$ activate at more hyperpolarized membrane potentials and generate much larger currents than those consisting of Na_v1.8 alone, upregulation of $\beta 3$ could contribute to injury-induced hyperexcitability.

The spontaneous electrogenesis in neuropathic pain has obvious similarities to that in epilepsy. In fact, there are alterations in Na⁺ channel expression, including upregulation of Na_v1.3 and changes in β subunits, in both animal models of limbic epilepsy^{28–30} and human postmortem or surgically resected epileptic hippocampus³¹. These changes suggest that mechanisms underlying epileptic hyperexcitability may be similar to those underlying neuropathic pain; however, the Na⁺ channel types expressed in brain differ from those expressed in sensory neurons, and because it has not been possible to assess the redistribution of Na⁺ channel subunits within central neurons, the role of Na⁺ channels is less firmly established in epilepsy than in neuropathic pain.

Na⁺ channel-blocking AEDs such as phenytoin and carbamazepine are effective in pain states by virtue of the same selective block of high-frequency action-potential firing that accounts for their protective activity against seizures. In acute pain, phenytoin and carbamazepine, when locally administered, have antinociceptive activity that is substantially more potent than that of the Na⁺ channel-blocking local anesthetic lidocaine³². It has been proposed that

these AEDs show antihyperalgesic activity in chronic pain by counteracting the hyperexcitability generated by the pathological expression and redistribution of Na⁺ channels³³. For example, carbamazepine at the serum concentrations used to treat trigeminal neuralgia and other painful neuropathies in humans has been reported to inhibit the generation of spontaneous ectopic impulses from experimental neuromas³⁴.

In addition to the peripheral changes that occur after nerve injury, spinal cord neurons show a progressive increase in responsiveness with repeated activation of C-fibers, known as 'wind-up', that is considered to underlie the phenomenon of 'central sensitization' (hyperexcitability of spinal nociceptive neurons after peripheral damage). Na⁺ channel blockers such as lidocaine can suppress wind-up³⁵, although Na⁺ channel-blocking AEDs have not so far been shown to inhibit the phenomenon³⁶. In spinal dorsal horn neurons, Ca²⁺-dependent plateau potentials have been implicated in the generation of wind-up³⁷. Consequently, AEDs that target high voltage-activated Ca²⁺ channels, such as gabapentin, lamotrigine, oxcarbazepine and lamotrigine³¹, could suppress these plateau potentials and contribute to antineuropathic pain action.

Role of Ca²⁺ channels. Selective alterations in the expression of Ca²⁺ channel subunits occur in some models of chronic neuropathic pain³⁸. After peripheral nerve ligation injury the $\alpha 2\delta$ -1 subunit in dorsal root ganglion neurons is markedly upregulated in association with the development of tactile allodynia^{39,40} (Figs. 1b,c and 2). The allodynia in this model is sensitive to gabapentin, although this drug does not have a general analgesic effect. Similarly, gabapentin inhibits ectopic discharges of pain fibers after nerve injury⁴¹ and attenuates the responses of spinal cord dorsal horn neurons to noxious stimulation in the post-injury state (but not in uninjured animals)^{42,43}, resulting in a reduction in experimental allodynia. Gabapentin binds with high affinity to $\alpha 2\delta$ -1 and $\alpha 2\delta$ -2 and is thought to inhibit high voltage-activated Ca²⁺ currents through channels that contain these subunits (reviewed in ref. 5; Fig. 1a).

Notably, $\alpha 2\delta$ is not upregulated in all models of hyperalgesia^{20,44}. In those situations where $\alpha 2\delta$ upregulation occurs in dorsal root ganglion neurons or in the spinal cord, however, gabapentin does show antiallodynic effects, supporting the view that gabapentin blocks neuropathic pain by inhibiting the excessive excitability in dorsal root ganglion neurons resulting from upregulation of $\alpha 2\delta$. The aforementioned ability of gabapentin to inhibit selectively dorsal horn neuron responses to nociceptive stimulation after nerve injury seems to occur by a presynaptic action⁴³; presumably, the drug functions by reducing transmitter release from excitatory afferents that are rendered drug sensitive because they contain high voltage-activated Ca²⁺ channels with $\alpha 2\delta$ subunits⁴⁵. Support for the concept that gabapentin acts in neuropathic pain through its interaction with $\alpha 2\delta$ comes from studies with

gabapentin analogs that show similar structural specificity for $\alpha 2\delta$ binding and activity against allodynia in animal models of neuropathic pain⁴⁶.

T-type low voltage-activated Ca²⁺ channels were first described in sensory neurons, and evidence indicates that these channels are involved in the transmission of neuropathic pain signals from peripheral nociceptors and in the spinal cord⁴⁷. Ethosuximide^{48,49} and zonisamide⁵⁰, which block T-type Ca²⁺ channels⁵, have beneficial effects in experimental models of neuropathic pain. In contrast to other AEDs, however, these drugs have not been reported to be useful in human neuropathic pain (Table 1). Indeed, recent evidence from $\alpha 1G$ knockout mice indicates that bursting in thalamocortical neurons mediated by T-type Ca²⁺ channels has an inhibitory role in pain transmission⁵¹. Consequently, at the level of the thalamus, T-channel blockers would be expected to reduce this endogenous antinociceptive action of the Ca²⁺ current, balancing any beneficial effect exerted in the periphery. T-channel blockers whose action is restricted to the periphery may be useful analgesics⁵².

Migraine

Migraine headache is another pain syndrome for which AEDs are commonly prescribed. Migraine is characterized by episodic pain, and the paroxysmal nature of the disorder is reminiscent of epilepsy. Pain in migraine results from the activation of trigeminovascular afferents from the meninges, which become sensitized in a way similar to their sensitization in other neurogenic pain states⁵³.

Substantial evidence now indicates that the trigeminovascular system is activated by cortical spreading depression, which results from neocortical hyperexcitability. The mechanisms that underlie the

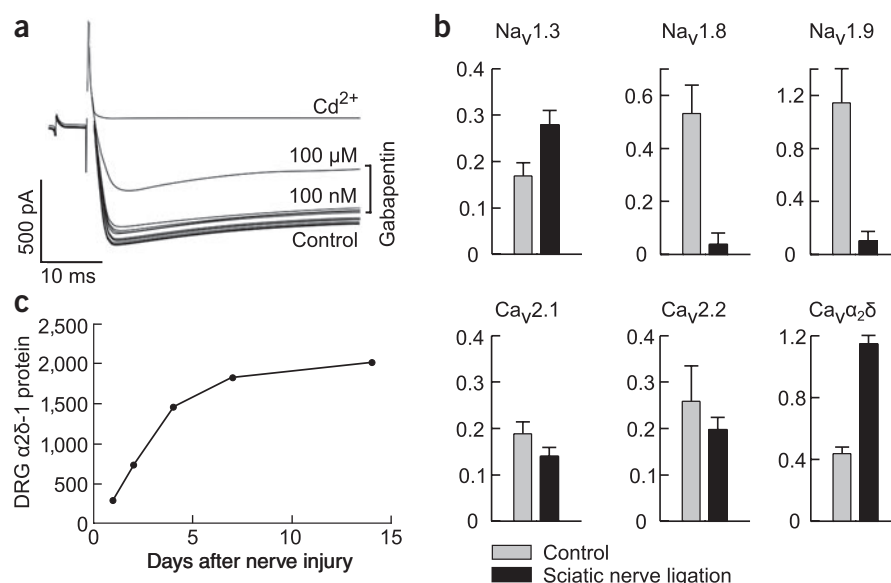


Figure 1 Gabapentin and Ca²⁺ channel subunit plasticity in chronic pain models. (a) Gabapentin inhibition of voltage-activated Ca²⁺ current in a rat sensory (dorsal root ganglion) neuron about 1 week after chronic constriction injury. Currents were elicited by depolarizing pulses from −85 mV to +30 mV. The current is partially depressed by gabapentin and completely blocked by 200 μM Cd²⁺. Reproduced with permission from ref. 114. (b) Quantification of Na⁺ and Ca²⁺ channel subunit mRNA by RT-PCR in a rat L5 dorsal root ganglion after spinal nerve ligation causing mechanical allodynia and thermal hyperalgesia. Values are normalized to β-actin mRNA. Reproduced with permission from ref. 20. (c) Time course of the increase in α₂δ-1 subunit protein in rat dorsal root ganglia after spinal nerve ligation, as assayed by western blotting. Results are given as a percentage of protein on the contralateral side. Reproduced with permission from ref. 44.

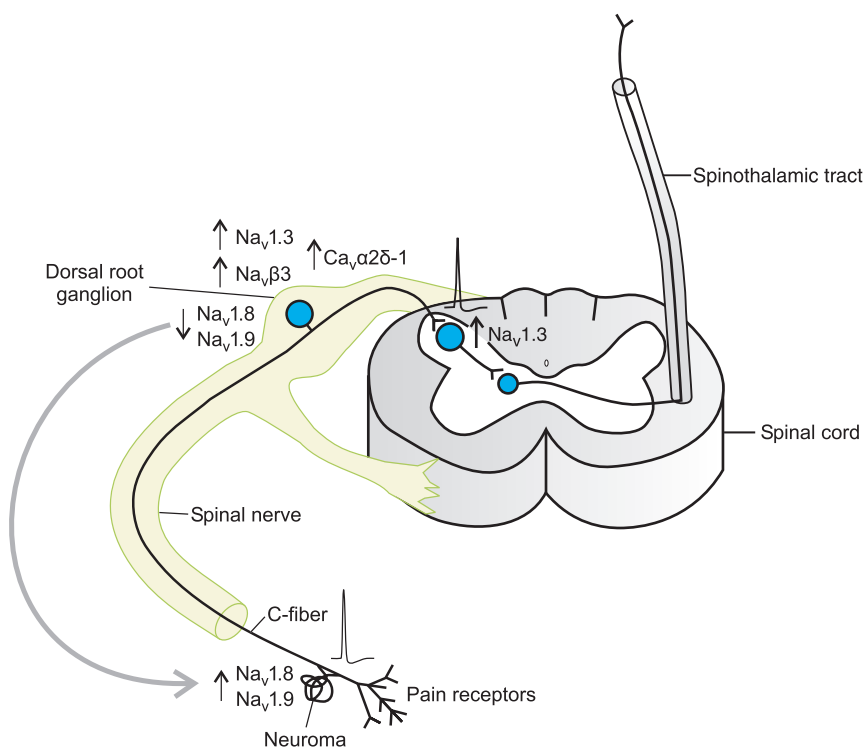


Figure 2 The peripheral and spinal cord afferent pain pathway, showing alterations in voltage-dependent Na^+ and Ca^{2+} channel subunits after chronic nerve injury associated with neuropathic pain. There is an increase in the expression of $\text{Na}_v1.3$ channels and Na^+ channel $\beta 3$ ($\text{Na}_v\beta 3$) and Ca^{2+} channel $\alpha 2\delta-1$ ($\text{Ca}_v\alpha 2\delta-1$) subunits in dorsal root ganglion neuron cell bodies, and in the expression of $\text{Na}_v1.3$ in second-order nociceptive neurons in the spinal cord dorsal horn. The tetrodotoxin-resistant Na^+ channel subunits $\text{Na}_v1.8$ and $\text{Na}_v1.9$ are also redistributed from dorsal root ganglion neuron cell bodies to peripheral axons and pain receptors at the site of injury. These changes are thought to result in spontaneous ectopic discharges and lower the threshold for mechanical activation that leads to paraesthesias, hyperalgesia and allodynia.

cortical hyperexcitability are unknown, but the phenomenon could be related to excessive excitatory transmitter release resulting from alterations in Ca^{2+} channel function, as occurs in familial hemiplegic migraine—an autosomal-dominant form of migraine associated with mutations in the Ca^{2+} channel $\alpha 1A$ subunit⁵⁴.

Valproate is the only AED currently approved in the United States for migraine therapy, but recent controlled trials have shown that topiramate and gabapentin also reduce the frequency of migraine attacks^{55,56} and several other AEDs seem to be promising (Table 1). These AEDs might act by ameliorating excessive activity in sensitized trigeminal sensory fibers through their effects on Na^+ and Ca^{2+} channels, as in other pain states. They could also inhibit the release of inflammatory mediators, such as calcitonin gene-related peptide, that are involved in pain generation. In addition, AEDs could act more proximately by specifically interfering with the neuronal hyperexcitability that leads to cortical spreading depression, perhaps by modulating the release of glutamate, inhibiting glutamate-mediated excitation postsynaptically (as in the case of topiramate, which acts on kainate and AMPA receptors) or by enhancing inhibition⁵.

Neuromuscular syndromes

Although they have variable efficacy, AEDs are used to treat numerous movement disorders and neuromuscular syndromes including nonepileptic myoclonus, essential tremor, paroxysmal types of dyskinesias such as paroxysmal kinesigenic dyskinesia or choreoatheto-

sis^{57–60} and various forms of myotonia (Table 1). The molecular basis of most of these disorders is unknown; however, several episodic muscle disorders—for example, potassium-aggravated myotonia, cold-aggravated myotonia, paramyotonia congenita and hyperkalemic periodic paralysis—are now known to be caused by mutations that interfere with fast inactivation of the skeletal muscle Na^+ channel α subunit SCN4A, leading to sarcolemmal hyperexcitability.

These syndromes (particularly potassium-aggravated myotonia and paramyotonia congenita) are responsive to local anesthetics such as mexiletine that act in a manner similar to that of Na^+ channel blocking AEDs to enhance Na^+ channel inactivation and thus to 'reverse' the defect in channel function⁶¹. However, such agents are only modestly effective. This low efficacy may be explained by the fact that the anomalous spontaneous discharges of muscle fibers in myotonia do not occur at abnormally high rates, so that muscle Na^+ channels cannot accumulate the degree of drug block that occurs in neuronal Na^+ channels during epileptic discharges⁶².

Antiepileptic drugs, especially phenytoin and carbamazepine, are useful in treating acquired neuromyotonia (Issacs' syndrome), a condition in which there is continuous rippling movements of the muscles under the skin (myokymia)^{63,64}. The disorder is due to abnormal activity in the distal portion of motor nerves resulting from autoantibodies to voltage-activated K^+ channels. In many cases, AEDs completely resolve the

myokymia. Similarly, AEDs, including acetazolamide and phenytoin, can be useful in treating the myokymia that occurs in episodic ataxia, an inherited form of neuromyotonia associated with brief attacks of cerebellar ataxia due to mutations in the Shaker-type K^+ channel subunit hKv1.1 (KCNA1)^{65,66}. Notably, KCNA1 is expressed in the juxtaparanodal region of motor neuron axons as well as in the initial segments, dendrites and presynaptic nerve terminals of neurons in the cerebellum and hippocampus. Thus, these channels are appropriately placed to account for the neuromyotonia and cerebellar dysfunction and also the seizures that occur in some forms of episodic ataxia⁶⁷.

Antiepileptic drugs that enhance GABA-mediated inhibition often show utility in clinical neurology and psychiatry. For example, benzodiazepines, primidone and topiramate are effective for treating essential tremor⁶⁸ and nonepileptic myoclonus⁶⁹. Hyperekplexia (startle disease)—a rare nonepileptic disorder characterized by an exaggerated persistent startle reaction, generalized muscular rigidity and nocturnal myoclonus owing to a genetic defect in the glycine receptor—also responds to benzodiazepines^{70,71}. Glycine receptors are ligand-gated ion channels that, similar to GABA_A receptors, are permeable to Cl^- ions and participate, along with GABA_A receptors, in fast synaptic inhibition in the spinal cord and brainstem. The positive modulatory effects of benzodiazepines on GABA_A receptors presumably compensate for the defective glycine receptor function in hyperekplexia.

Bipolar affective disorder

Randomized controlled clinical trials have shown that carbamazepine, oxcarbazepine, lamotrigine and valproate are effective for treating bipolar affective disorder⁷² (Table 1). The delayed clinical efficacy of AEDs in mood disorders suggests that the underlying mechanisms may be distinct from those that are relevant to epilepsy, pain syndromes and neuromuscular disorders.

The molecular origins of bipolar disorder are unknown and the mechanistic basis of mood stabilizer therapies is similarly obscure⁷³. Nevertheless, accumulating evidence from brain imaging and post-mortem histopathology indicates that there is regional brain atrophy in mood disorders, leading to the view that atrophy or death of glia or neurons could be central to the pathophysiology^{74,75}. It has been further proposed that mood-stabilizing drugs may exert beneficial actions by attenuating or reversing disease-related impairments in neuronal plasticity, neurogenesis or cell survival. In this regard, it is notable that some AEDs, including valproate and topiramate, have neuroprotective effects, for example, in animal models of stroke or status epilepticus^{76–78}.

One approach to determining how AEDs exert beneficial effects in mood disorders is to identify targets that AEDs share with lithium, which has been the gold standard in the treatment and prophylaxis of bipolar disorder since its introduction in the 1950s (ref. 79). Berridge *et al.*⁸⁰ have suggested that depletion of inositol by inhibition of the enzymatic breakdown of inositol phosphates to free inositol is the mechanism underlying the mood-stabilizing action of lithium (Fig. 3a). The resulting reduction of free intracellular inositol is proposed to slow the recycling of inositol-containing metabolites required for signal transduction.

As with lithium, the mood-stabilizing action of valproate and carbamazepine has been linked to inositol depletion^{80–83}. This effect is considered to result in stabilization of the structural integrity of neurons and enhancement of synaptic plasticity⁸⁴. The mood-stabilizing effects of lithium have been also attributed to the inhibition of glycogen synthase kinase 3 β (GSK3 β), an enzyme that contributes to many cellular functions including apoptosis⁸⁵. Lamotrigine⁸⁵ and valproate⁸⁶ have similar effects on GSK3 β , whereas carbamazepine does not. Carbamazepine may produce comparable functional effects by influencing signaling mechanisms upstream of GSK3 β (ref. 87). Other common actions of lithium and valproate are to increase the activity of the extracellular signal-regulated kinase (ERK) pathway, which is involved in the differentiation, survival and structural and functional plasticity of neurons^{88,89} (Fig. 3b). It has been proposed that lithium and valproate promote neuronal survival and exert their antimanic effects through diverse effects on cell signaling⁹⁰.

In summary, mood disorders may be associated with a disruption in mechanisms that govern cell survival and neural plasticity, and emerging evidence now suggests that AEDs with mood-stabilizing activity can affect signaling pathways to reverse these pathological events. Because these signaling systems are involved in embryogenesis and development, it is intriguing to speculate that such actions could account for the well-recognized teratogenic effects of the AEDs.

Schizophrenia

In addition to their actions in mood disorders, several AEDs, including carbamazepine, benzodiazepines, lamotrigine and particularly valproate, may be efficacious in the treatment of neuroleptic-resistant

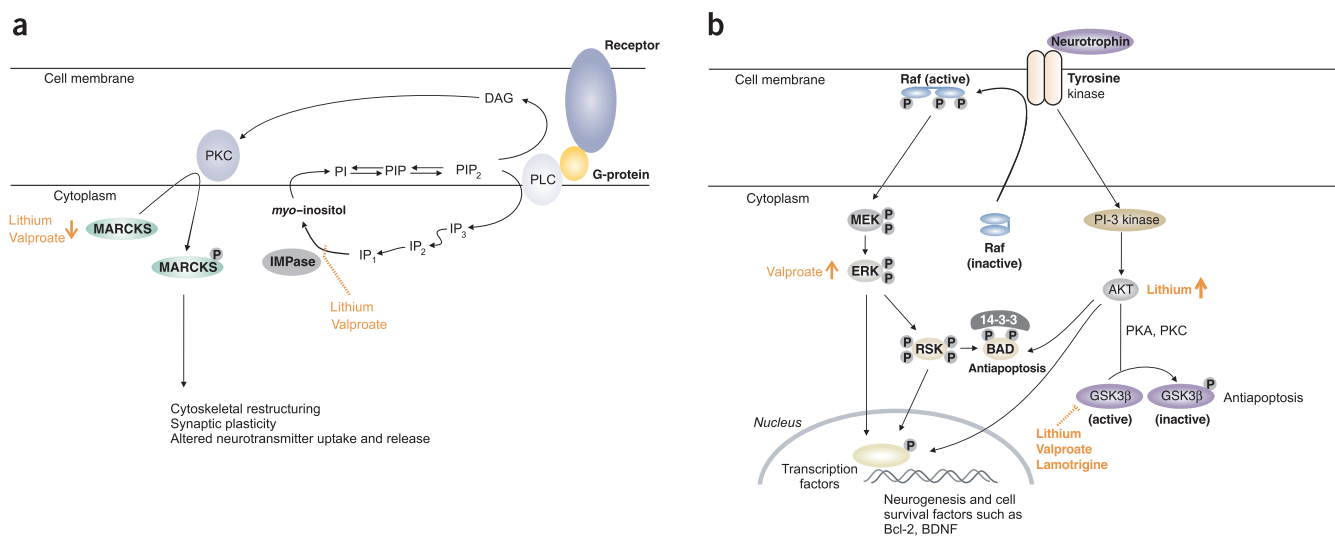


Figure 3 Common effects of AEDs and lithium on cell signaling thought to contribute to long-term effects in mood disorders. **(a)** In the phosphoinositol (PI) cycle, lithium and valproate block inositol monophosphatase (IMPase), preventing conversion of inositol-1-phosphate (IP₁) to *myo*-inositol. This leads to accumulation of inositol monophosphates and depletion of *myo*-inositol, which reduces phosphatidylinositol-4,5-bisphosphate (PIP₂) and its cleavage products inositol-1,4,5-triphosphate (IP₃) and diacylglycerol (DAG), an activator of protein kinase C (PKC). Dampening the PI cycle with lithium treatment downregulates PKC isozymes. Among PKC substrates, myristoylated alanine-rich C-kinase substrate (MARCKS) is particularly relevant. MARCKS is an actin-binding protein expressed in neurites and implicated in cytoskeletal restructuring; its expression is downregulated by lithium and valproate, thereby stabilizing neuronal integrity. **(b)** In the ERK/mitogen-activated protein (MAP) kinase signaling cascade, valproate activates ERK, resulting in enhanced transcription of neurogenesis and cell survival factors such as antiapoptotic protein Bcl-2 and the neurotrophin BDNF. Also activated is ERK-regulated kinase (RSK), which phosphorylates the proapoptotic protein Bcl-2/Bcl_x-associated death promoter (BAD), enabling it to bind 14-3-3 proteins that tether it in the cytoplasm and thereby impair its ability to antagonize the protective functions of Bcl-2. RSK also activates transcription factors that positively influence survival. Upstream, ERK is activated by Raf and MAP kinase kinase (MEK). GSK3 β is a serine/threonine kinase that influences many cellular processes and is downregulated by lithium and AEDs. Inhibition of GSK3 β is thought to influence gene transcription, leading to antiapoptotic effects and improved cell structural stability. (See text for references.)

schizophrenia^{91,92}. Recent data suggest that valproate is a potent inhibitor of histone deacetylases^{93,94}, which act as negative regulators of gene expression. Through an action on histone deacetylases, valproate has been found to counteract experimentally induced down-regulation of reelin, a neuronal migration factor, and GAD₆₇, a key enzyme in GABA synthesis; deficiencies of these proteins have been implicated in the pathogenesis of schizophrenia^{95,96}. Indeed, reduced amounts of prefrontal cortical GAD₆₇ are among the most robust and diagnostically specific findings in postmortem studies of the schizophrenic brain^{97–99}. Valproate could abrogate these pathological changes and it has been proposed that this might contribute to its antipsychotic activity¹⁰⁰.

Perspective

Antiepileptic drugs were found to be useful in pain medicine, psychiatry and the treatment of other nonepileptic conditions largely by serendipity and, until recently, the mechanisms underlying their beneficial actions in these conditions were obscure. Considerable advances have come from studies using models of chronic neuropathic pain. It is now recognized that hyperalgesia and allodynia develop as a result of the pathological plasticity of Na⁺ and Ca²⁺ channels: namely, the redistribution of channels within neurons and alterations in the expression of specific subunits.

The enhanced pathological excitability can be counteracted by AEDs that act specifically on channels responsible for the injury-related abnormal activity; this counteraction occurs in a use-dependent fashion such that pathological high-frequency firing is affected more than ordinary activity. In addition, for gabapentin at least, drug binding occurs specifically to a pathologically overexpressed subunit. Together, these factors provide AEDs with the ability to suppress aberrant neuronal firing with minimal effects on normal ongoing activity. The underlying mechanisms through which the drugs act in neuropathic pain are similar to those in epilepsy⁵; at present, however, the molecular pathophysiological mechanisms are better established for chronic pain.

In psychiatric conditions, most notably bipolar affective disorder, emerging evidence now indicates that the long-term therapeutic activity of some AEDs may involve effects on intracellular second-messenger systems such the ERK signaling cascade. The ultimate effects of these actions are postulated to be not alterations in neuronal excitability, but rather beneficial effects on the structural integrity of neurons and the enhancement of synaptic plasticity. These drug actions seem to differ fundamentally from the better-understood effects of AEDs on neuronal firing and synaptic activity that are relevant in epilepsy; indeed, the relationship, if any, between the two distinct types of activity is uncertain. Unraveling the mechanisms that underlie the long-term beneficial effects in psychiatric conditions is one of the most crucial challenges for AED research.

COMPETING INTEREST STATEMENT

The authors declare that they have no competing financial interests.

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1. Löscher, W. & Schmidt, D. New horizons in the development of antiepileptic drugs. *Epilepsy Res.* **50**, 3–16 (2002).
2. Fromm, G.H. Antiepileptic actions of carbamazepine. in *Drugs for Control of Epilepsy: Actions on Neuronal Networks Involved in Seizure Disorders* (eds. Faingold, C.L. & Fromm, G.H.) 425–436 (CRC Press, Boca Raton, Florida, USA, 1992).
3. Silberstein, S.D. Shared mechanisms and comorbidities in neurologic and

4. psychiatric disorders. *Headache* **41** (suppl. 1), S11–S17 (2001).
5. Ottman, R. & Lipton, R.B. Comorbidity of migraine and epilepsy. *Neurology* **44**, 2105–2110 (1994).
6. Rogawski, M.A. & Löscher, W. The neurobiology of antiepileptic drugs. *Nat. Rev. Neurosci.* **5**, 553–564 (2004).
7. Rudolph, U. & Möhler, H. Analysis of GABA_A receptor function and dissection of the pharmacology of benzodiazepines and general anesthetics through mouse genetics. *Annu. Rev. Pharmacol. Toxicol.* **44**, 475–498 (2004).
8. French-Mullen, J.M.H., Barker, J.L. & Rogawski, M.A. Calcium current block by (–)-pentobarbital, phenobarbital and CHEB but not (+)-pentobarbital in acutely isolated CA1 neurons: comparison with effects on GABA-activated Cl[–] current. *J. Neurosci.* **13**, 3211–3221 (1993).
9. Pollack, M.H., Matthews, J. & Scott, E.L. Gabapentin as a potential treatment for anxiety disorders. *Am. J. Psychiatry* **155**, 992–993 (1998).
10. Pande, A.C. et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J. Clin. Psychopharmacol.* **19**, 341–348 (1999).
11. de-Paris, F. et al. Effects of gabapentin on anxiety induced by simulated public speaking. *J. Psychopharmacol.* **17**, 184–188 (2003).
12. Ross EL. The evolving role of antiepileptic drugs in treating neuropathic pain. *Neurology* **55** (suppl. 1), S41–S46 (2000).
13. Eisenberg, E., Alon, N., Ishay, A., Daoud, D. & Yarnitsky, D. Lamotrigine in the treatment of painful diabetic neuropathy. *Eur. J. Neurol.* **5**, 167–173 (1998).
14. Nicholson, B. Gabapentin use in neuropathic pain syndromes. *Acta Neurol. Scand.* **101**, 359–371 (2000).
15. Pappagallo, M. Newer antiepileptic drugs: possible uses in the treatment of neuropathic pain and migraine. *Clin. Ther.* **25**, 2506–2538 (2003).
16. Rozen, T.D. Antiepileptic drugs in the management of cluster headache and trigeminal neuralgia. *Headache* **41** (suppl. 1), S25–S32 (2001).
17. Beydoun, A. & Backonja, M.M. Mechanistic stratification of antineuralgic agents. *J. Pain Symptom. Manage.* **25**, S18–S30 (2003).
18. Dib-Hajj, S.D. et al. Plasticity of sodium channel expression in DRG neurons in the chronic constriction injury model of neuropathic pain. *Pain* **83**, 591–600 (1999).
19. Kim, C.H., Oh, Y., Chung, J.M. & Chung, K. The changes in expression of three subtypes of TTX sensitive sodium channels in sensory neurons after spinal nerve ligation. *Brain Res. Mol. Brain Res.* **95**, 153–161 (2001).
20. Craner, M.J., Klein, J.P., Renganathan, M., Black, J.A. & Waxman, S.G. Changes of sodium channel expression in experimental painful diabetic neuropathy. *Ann. Neurol.* **52**, 786–792 (2002).
21. Abe, M., Kurihara, T., Han, W., Shinomiya, K. & Tanabe, T. Changes in expression of voltage-dependent ion channel subunits in dorsal root ganglia of rats with radicular injury and pain. *Spine* **27**, 1517–1524 (2002).
22. Gold, M.S. et al. Redistribution of Na_v1.8 in uninjured axons enables neuropathic pain. *J. Neurosci.* **23**, 158–166 (2003).
23. Hains, B.C. et al. Upregulation of sodium channel Nav1.3 and functional involvement in neuronal hyperexcitability associated with central neuropathic pain after spinal cord injury. *J. Neurosci.* **23**, 8881–8892 (2003).
24. Cummins, T.R. et al. Nav1.3 sodium channels: rapid repriming and slow closed-state inactivation display quantitative differences after expression in a mammalian cell line and in spinal sensory neurons. *J. Neurosci.* **21**, 5952–5961 (2001).
25. Novakovic, S.D. et al. Distribution of the tetrodotoxin-resistant sodium channel PN3 in rat sensory neurons in normal and neuropathic conditions. *J. Neurosci.* **18**, 2174–2187 (1998).
26. Roza, C., Laird, J.M., Souslova, V., Wood, J.N. & Cervero, F. The tetrodotoxin-resistant Na⁺ channel Na_v1.8 is essential for the expression of spontaneous activity in damaged sensory axons of mice. *J. Physiol. (Lond.)* **550**, 921–926 (2003).
27. Shah, B.S. et al. β3, a novel auxiliary subunit for the voltage-gated sodium channel, is expressed preferentially in sensory neurons and is upregulated in the chronic constriction injury model of neuropathic pain. *Eur. J. Neurosci.* **12**, 3985–3990 (2000).
28. Shah, B.S. et al. β3, a novel auxiliary subunit for the voltage gated sodium channel is upregulated in sensory neurones following streptozocin induced diabetic neuropathy in rat. *Neurosci. Lett.* **309**, 1–4 (2001).
29. Bartolomei, F. et al. Changes in the mRNAs encoding subtypes I, II and III sodium channel α subunits following kainate-induced seizures in rat brain. *J. Neurocytol.* **26**, 667–678 (1997).
30. Aronica, E. et al. Induction of neonatal sodium channel II and III α isoform mRNAs in neurons and microglia after status epilepticus in the rat hippocampus. *Eur. J. Neurosci.* **13**, 1261–1266 (2001).
31. Ellerkmann, R.K. et al. Molecular and functional changes in voltage-dependent Na⁺ channels following pilocarpine-induced status epilepticus in rat dentate granule cells. *Neuroscience* **119**, 323–333 (2003).
32. Whitaker, W.R. et al. Changes in the mRNAs encoding voltage-gated sodium channel types II and III in human epileptic hippocampus. *Neuroscience* **106**, 275–285 (2001).
33. Todorovic, S.M., Rastogi, A.J. & Jevtovic-Todorovic, V. Potent analgesic effects of anticonvulsants on peripheral thermal nociception in rats. *Brit. J. Pharmacol.* **140**, 255–260 (2003).
34. Rizzo, M.A. Successful treatment of painful traumatic mononeuropathy with carbamazepine: insights into a possible molecular pain mechanism. *J. Neurol. Sci.* **152**, 103–106 (1997).
35. Burchiel, K.J. Carbamazepine inhibits spontaneous activity in experimental

- neuromas. *Exp. Neurol.* **102**, 249–253 (1988).
35. Herrero, J.F., Laird, J.M. & Lopez-Garcia, J.A. Wind-up of spinal cord neurones and pain sensation: much ado about something? *Prog. Neurobiol.* **61**, 169–203 (2000).
 36. Chapman, V., Wildman, M.A. & Dickenson, A.H. Distinct electrophysiological effects of two spinally administered membrane stabilising drugs, bupivacaine and lamotrigine. *Pain* **71**, 285–295 (1997).
 37. Murakami, M. *et al.* Pain perception in mice lacking the $\beta 3$ subunit of voltage-activated calcium channels. *J. Biol. Chem.* **277**, 40342–40351 (2002).
 38. Cizkova, D. *et al.* Localization of N-type Ca^{2+} channels in the rat spinal cord following chronic constrictive nerve injury. *Exp. Brain Res.* **147**, 456–463 (2002).
 39. Newton, R.A., Bingham, S., Case, P.C., Sanger, G.J. & Lawson, S.N. Dorsal root ganglion neurons show increased expression of the calcium channel $\alpha 2\delta$ -1 subunit following partial sciatic nerve injury. *Brain Res. Mol. Brain Res.* **95**, 1–8 (2001).
 40. Luo, Z.D. *et al.* Upregulation of dorsal root ganglion $\alpha 2\delta$ calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. *J. Neurosci.* **21**, 1868–1875 (2001).
 41. Pan, H.-L., Eisenach, J.C. & Chen, S.-R. Gabapentin suppresses ectopic nerve discharges and reverses allodynia in neuropathic rats. *J. Pharmacol. Exp. Ther.* **288**, 1026–1030 (1999).
 42. Stanfa, L.C., Singh, L., Williams, R.G. & Dickenson, A.H. Gabapentin, ineffective in normal rats, markedly reduces C-fibre evoked responses after inflammation. *NeuroReport* **8**, 587–590 (1997).
 43. Patel, M.K., Gonzalez, M.I., Bramwell, S., Pinnock, R.D. & Lee, K. Gabapentin inhibits excitatory synaptic transmission in the hyperalgesic spinal cord. *Br. J. Pharmacol.* **130**, 1731–1734 (2000).
 44. Luo, Z.D. *et al.* Injury type-specific calcium channel $\alpha 2\delta$ -1 subunit up-regulation in rat neuropathic pain models correlates with antiallodynic effects of gabapentin. *J. Pharmacol. Exp. Ther.* **303**, 1199–1205 (2002).
 45. Shimoyama, M., Shimoyama, N. & Hori, Y. Gabapentin affects glutamatergic excitatory neurotransmission in the rat dorsal horn. *Pain* **85**, 405–414 (2000).
 46. Field, M.J., Hughes, J. & Singh, L. (2000) Further evidence for the role of the $\alpha 2\delta$ subunit of voltage dependent calcium channels in models of neuropathic pain. *Brit. J. Pharmacol.* **131**, 282–286 (2000).
 47. Todorovic, S.M. *et al.* Redox modulation of T-type calcium channels in rat peripheral nociceptors. *Neuron* **31**, 75–85 (2001).
 48. Dogrul, A. *et al.* Reversal of experimental neuropathic pain by T-type calcium channel blockers. *Pain* **105**, 159–168 (2003).
 49. Matthews, E.A. & Dickenson, A.H. Effects of ethosuximide, a T-type Ca^{2+} channel blocker, on dorsal horn neuronal responses in rats. *Eur. J. Pharmacol.* **415**, 141–149 (2001).
 50. Hord, A.H., Denson, D.D., Chalfoun, A.G. & Azevedo, M.I. The effect of systemic zonisamide (Zonegran) on thermal hyperalgesia and mechanical allodynia in rats with an experimental mononeuropathy. *Anesth. Analg.* **96**, 1700–1706 (2003).
 51. Kim, D. *et al.* Thalamic control of visceral nociception mediated by T-type Ca^{2+} channels. *Science* **302**, 117–119 (2003).
 52. Todorovic, S.M., Meyenburg, A. & Jevtovic-Todorovic, V. Mechanical and thermal antinociception in rats following systemic administration of mibefradil, a T-type calcium channel blocker. *Brain Res.* **951**, 336–340 (2002).
 53. Pietronbon, D. & Striessnig, J. Neurobiology of migraine. *Nat. Rev. Neurosci.* **4**, 386–398 (2003).
 54. Randall, A. & Benham, C.D. Recent advances in the molecular understanding of voltage-gated Ca^{2+} channels. *Mol. Cell. Neurosci.* **14**, 255–272 (1999).
 55. Mathew, N.T. Antiepileptic drugs in migraine prevention. *Headache* **41** (suppl. 1), S18–S24 (2001).
 56. Brandes, J.L. *et al.* Topiramate for migraine prevention: a randomized controlled trial. *JAMA* **291**, 965–973 (2004).
 57. Chudnow, R.S., Mimbel, R.A., Owen, D.B. & Roach, E.S. Gabapentin for familial paroxysmal dystonic choreoathetosis. *Neurology* **49**, 1441–1442 (1997).
 58. Richter, A. & Löscher, W. Gabapentin decreases the severity of dystonia at low doses in a genetic animal model of paroxysmal dystonic choreoathetosis. *Eur. J. Pharmacol.* **369**, 335–338.
 59. Fukuda, M., Hashimoto, O., Nagakubo, S. & Hata, A. A family with an atonic variant of paroxysmal kinesigenic choreoathetosis and hypercalcitoninemia. *Mov. Disord.* **14**, 342–344 (1999).
 60. Lotze, T. & Jankovic, J. Paroxysmal kinesigenic dyskinesias. *Semin. Pediatr. Neurol.* **2003** **10**, 68–79 (2003).
 61. Beech, J., Fletcher, J.E., Tripolitis, L. & Lindborg, S. Effects of phenytoin in two myotonic horses with hyperkalemic periodic paralysis. *Muscle Nerve* **15**, 932–936 (1992).
 62. Cannon, S.C. From mutation to myotonia in sodium channel disorders. *Neuromuscul. Disord.* **7**, 241–249 (1997).
 63. Caress, J.B. & Walker, F.O. The spectrum of ectopic motor nerve behavior: from fasciculations to neuromyotonia. *Neurologist* **8**, 41–46 (2002).
 64. Oh, S.J., Alapati, A., Claussen, G.C. & Vernino, S. Myokymia, neuromyotonia, dermatomyositis, and voltage-gated K^{+} channel antibodies. *Muscle Nerve* **27**, 757–760 (2003).
 65. McGuire, S.A., Tomasovic, J.J. & Ackerman, N. Jr. Hereditary continuous muscle fiber activity. *Arch. Neurol.* **41**, 395–396 (1984).
 66. Lubbers, W.J. *et al.* Hereditary myokymia and paroxysmal ataxia linked to chromosome 12 is responsive to acetazolamide. *J. Neurol. Neurosurg. Psychiatry* **59**, 400–405 (1995).
 67. Kullmann, D.M. The neuronal channelopathies. *Brain* **125**, 1177–1195 (2002).
 68. Pahwa, R. & Lyons, K.E. Essential tremor: differential diagnosis and current therapy. *Am. J. Med.* **115**, 134–142 (2003).
 69. Connor, G.S. A double-blind placebo-controlled trial of topiramate treatment for essential tremor. *Neurology* **59**, 132–134 (2002).
 70. Praveen, V., Patole, S.K. & Whitehall, J.S. Hyperekplexia in neonates. *Postgrad. Med. J.* **77**, 570–572 (2001).
 71. Zhou, L., Chillag, K.L. & Nigro, M.A. Hyperekplexia: a treatable neurogenetic disease. *Brain Dev.* **24**, 669–674 (2002).
 72. Muzina, D.J., El-Sayegh, S. & Calabrese, J.R. Antiepileptic drugs in psychiatry—focus on randomized controlled trial. *Epilepsy Res.* **50**, 195–202 (2002).
 73. Harwood, A.J. & Agam, G. Search for a common mechanism of mood stabilizers. *Biochem. Pharmacol.* **66**, 179–189 (2003).
 74. Manji, H.K. & Duman, R.S. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. *Psychopharmacol. Bull.* **35**, 5–49 (2001).
 75. Coyle, J.T. & Duman, R.S. Finding the intracellular signaling pathways affected by mood disorder treatments. *Neuron* **38**, 157–160 (2003).
 76. Löscher, W. Animal models of epilepsy for the development of antiepileptogenic and disease-modifying drugs. A comparison of the pharmacology of kindling and models with spontaneous recurrent seizures. *Epilepsy Res.* **50**, 105–123 (2002).
 77. Löscher, W. Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. *CNS Drugs* **16**, 669–694 (2002).
 78. Pitkänen, A. Efficacy of current antiepileptics to prevent neurodegeneration in epilepsy models. *Epilepsy Res.* **50**, 141–160 (2002).
 79. Williams, R.S., Cheng, L., Mudge, A.W. & Harwood, A.J. A common mechanism of action for three mood-stabilizing drugs. *Nature* **417**, 292–295 (2002).
 80. Berridge, M.J., Downes, C.P. & Hanley, M.R. Neural and developmental actions of lithium: a unifying hypothesis. *Cell* **59**, 411–419 (1989).
 81. Lubrich, B. & van Calcar, D. Inhibition of the high affinity myo-inositol transport system: a common mechanism of action of antipsychotic drugs? *Neuropsychopharmacology* **21**, 519–529 (1999).
 82. O'Donnell, T. *et al.* Chronic lithium and sodium valproate both decrease the concentration of myo-inositol and increase the concentration of inositol monophosphates in rat brain. *Brain Res.* **880**, 84–91 (2000).
 83. Vaden, D.L., Ding, D., Peterson, B. & Greenberg, M.L. Lithium and valproate decrease inositol mass and increase expression of the yeast *INO1* and *INO2* genes for inositol biosynthesis. *J. Biol. Chem.* **276**, 15466–15471 (2001).
 84. Lenox, R.H. & Wang, L. Molecular basis of lithium action: integration of lithium-responsive signaling and gene expression networks. *Mol. Psychiatry* **8**, 135–144 (2003).
 85. Li, X., Bijur, G.N. & Jope, R.S. Glycogen synthase kinase-3 β , mood stabilizers, and neuroprotection. *Bipolar Disord.* **4**, 137–144 (2002).
 86. Chen, G., Huang, L.D., Jiang, Y.M. & Manji, H.K. The mood-stabilizing agent valproate inhibits the activity of glycogen synthase kinase-3. *J. Neurochem.* **72**, 1327–1330 (1999).
 87. Mai, L., Jope, R.S. & Li, X. BDNF-mediated signal transduction is modulated by GSK3 β and mood stabilizing agents. *J. Neurochem.* **82**, 75–83 (2002).
 88. Yuan, P.X. *et al.* The mood stabilizer valproic acid activates mitogen-activated protein kinases and promotes neurite growth. *J. Biol. Chem.* **276**, 31674–31683 (2001).
 89. Einat, H. *et al.* The role of the extracellular signal-regulated kinase signaling pathway in mood modulation. *J. Neurosci.* **23**, 7311–7316 (2003).
 90. Manji, H.K., Drevets, W.C. & Charney, D.S. The cellular neurobiology of depression. *Nat. Med.* **7**, 541–547 (2001).
 91. Winterer, G. & Hermann, W.M. Valproate and the symptomatic treatment of schizophrenia spectrum patients. *Pharmacopsychiatry* **33**, 182–188 (2000).
 92. Hosak, L. & Libiger, J. Antiepileptic drugs in schizophrenia: a review. *Eur. Psychiatry* **17**, 371–378 (2002).
 93. Göttlicher, M. *et al.* Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. *EMBO J.* **20**, 6969–6978 (2001).
 94. Phiel, C.J. *et al.* Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. *J. Biol. Chem.* **276**, 36734–36741 (2001).
 95. Guidotti, A., Pesold, C. & Costa, E. (2000) New neurochemical markers for psychosis: a working hypothesis of their operation. *Neurochem. Res.* **25**, 1207–1218 (2000).
 96. Tremolizzo, L. *et al.* An epigenetic mouse model for molecular and behavioral neuropathologies related to schizophrenia vulnerability. *Proc. Natl. Acad. Sci. USA* **99**, 17095–17100 (2002).
 97. Akbarian, S. *et al.* Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. *Arch. Gen. Psychiatry* **52**, 258–266 (1995).
 98. Volk, D.W., Austin, M.C., Pierri, J.N., Sampson, A.R. & Lewis, D.A. Decreased GAD67 mRNA expression in a subset of prefrontal cortical GABA neurons in subjects with schizophrenia. *Arch. Gen. Psychiatry* **57**, 237–245 (2000).

99. Blum, B.P. & Mann, J.J.. The GABAergic system in schizophrenia. *Int. J. Neuropsychopharmacol.* **5**, 159–179 (2002).
100. Costa, E., Davis, J., Pesold, C., Tueting, P. & Guidotti, A. The heterozygote reeler mouse as a model for the development of a new generation of antipsychotics. *Curr. Opin. Pharmacol.* **2**, 56–62 (2002).
101. Drake, M.E. *et al.* Levetiracetam for preventive treatment of migraine. *Cephalalgia* **21**, 373 (2001).
102. Freitag, F.G., Diamond, S. & Solomon, G.D. The prophylaxis of migraine with the GABA-agonist tiagabine: a clinical report. *Headache* **19**, 354 (1999).
103. Gironell, A. *et al.* A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. *Arch. Neurol.* **56**, 474–480 (1999).
104. Sial, K.A., Malik, A. & Bajwa, Z. Small case series of gabitril (tiagabine) for prophylaxis of chronic daily headache with migrainous features. *Arch. Phys. Med. Rehabil.* **84**, E23 (2003).
105. Krusz, J.C. Levetiracetam as prophylaxis for resistant headaches. *Cephalalgia* **21**, 373 (2001).
106. Pande, A.C. *et al.* Treatment of social phobia with gabapentin: a placebo-controlled study. *J. Clin. Psychopharmacol.* **19**, 341–348 (1999).
107. Young, L.T. *et al.* Gabapentin as an adjunctive treatment in bipolar disorder. *J. Affect. Disord.* **55**, 73–77 (1999).
108. Happe, S., Sauter, C., Klosch, G., Saletu, B. & Zeitlhofer, J. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. *Neuropsychobiology* **48**, 82–86 (2003).
109. Anonymous. Gabapentin (Neurontin) for chronic pain. *Med. Lett. Drugs Ther.* **46**, 29–31 (2004).
110. Johnson, B.A. *et al.* Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. *Lancet* **361**, 1677–1685 (2003).
111. Myrick, H., Malcolm, R. & Anton, R. The use of antiepileptics in the treatment of addictive disorders. *Primary Psychiatry* **10**, 59–63 (2003).
112. Hoopes, S.P. *et al.* Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, part 1: improvement in binge and purge measures. *J. Clin. Psych.* **64**, 1335–1341 (2003).
113. McElroy, S.L. *et al.* Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. *Am. J. Psychiatry* **160**, 255–261 (2003).
114. Sarantopoulos, C., McCallum, B., Kwok, W.M. & Hogan, Q. Gabapentin decreases membrane calcium currents in injured as well as in control mammalian primary afferent neurons. *Reg. Anesth. Pain Med.* **27**, 47–57 (2002).